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Letter to the Editors

No association between the NDE1 gene and schizophrenia in the Japanese population

Dear Editors,

Series of studies have implicated that Disrupted in Schizophrenia 1 (DISC1) and its pathways are in the pathophysiology of schizophrenia (SZ) (Callicott et al., 2005; Hennah et al., 2003; Yamada et al., 2004). Recently, Hennah et al reported that the schizophrenic samples for the presence of SZ risk allelic haplotype (HEP3) of the DISC1 gene displayed an evidence for linkage of 16p13 (LOD=3.17) that contains the NDE1 gene. In addition, they also showed a significant association between specific haplotypes of the NDE1 gene (rs4781678-rs2242549-rs881803-rs2075512) and affected females with SZ spectrum disorders (Hennah et al., 2007). The NDE1 gene encodes a protein which interacts with the DISC1 protein (Millar et al., 2003; Brandon et al., 2004) and mouse models with NDE1 homozygous mutations displayed disordered cortex (Feng and Walsh, 2004). To confirm the association of the NDE1 gene with SZ, we performed the case-control association study in the Japanese population.

We used genomic DNA samples from 726 SZ patients: 406 male (mean age: 48.6±13.8 years), 320 female (mean age: 49.2±14.5 years) from the Tokushima University Hospital, affiliated psychiatric hospitals of the University of Tokushima, the Ehime University Hospital and the Osaka University Hospital in Japan. The diagnosis of SZ was made by at least two experienced psychiatrists according to DSM-IV criteria. 744 controls: 419 male (mean age: 45.8±11.3 years), 325 female (mean age: 45.2±10.5) were selected from volunteers without the psychiatric problems. All subjects were unrelated Japanese origin and signed written informed consent to participate in the genetic association studies approved by the institutional ethics committees. Genotyping was performed using commercially available TaqMan probes for the NDE1 gene with the Applied Biosystems 7500 Fast Real Time PCR System. We selected seven single nucleotide polymorphic (SNP) markers for genotyping from the public databases (dbSNP Home page) as reference for International Hap Map Project and Hennah's report (Hennah et al., 2007). The SNPs we selected includes six of seven of Hennah's because they are suitable for association study in the Japanese population. Haplotype block structure was determined using the HAPLOVIEW program (Barrett et al., 2005) defined according to the criteria of Gabriel et al. (Gabriel et al., 2002). Allelic and genotypic frequencies of patients and control subjects were compared using Fisher's exact test. The SNPAlyze 3.2Pro software (DYNACOM, Japan) was used to estimate haplotype frequencies, LD, permutation p values (10,000 replications) and deviation from Hardy–Weinberg (HW) distribution of alleles. Pair-wise LD indices (D' and r^2) were calculated for the control subjects. Power calculations for our sample size performed using the G*Power program (Erdfelder et al., 1996). The criterion for significance was set at $p<0.05$ for all tests.

Genotypic and allelic frequencies of the NDE1 gene are shown in Table 1. In power calculations using the G*Power program, our sample size had >0.97 power for detecting a significant association (alpha<0.05) when an effect size index of 0.2 was used. Genotypic distributions of these seven SNPs did not deviate significantly from HW equilibrium in either group ($p>0.05$). There were no significant differences in genotypic and allelic frequencies between cases and controls in all seven SNPs. LD between each pair of all the SNPs is relatively high ($D'\geqq 0.76$, $r^2\geqq 0.39$). There were two LD blocks in NDE1 with rs2242549 and rs881803 residing in block 1 and rs2075512 and rs2384933 residing in block 2. The two marker haplotypes of block 1 and block 2 were not associated with SZ (permutation $p=0.93$, 0.36, respectively). When the data were subdivided on the basis of gender, no significant association was observed in seven SNPs either in male or female samples. The two marker haplotypes of block 1 and block 2 were not associated with SZ either in male and female (permutation p of block 1=0.73 and 0.26, permutation p of block 2=0.49 and 0.21, respectively). In addition, a tag-haplotype (rs4781678-rs2242549-rs881803-rs2075512) that Hennah et al reported a significant association with SZ

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t1.1 Table 1
t1.2 Genotypes and allele frequencies for the seven polymorphism

t1.3 SNP	Total samples									Female			Male		
t1.4	Diagnosis	Allele		p-value genotype				p-value frequency		Allele		p-value	Allele		p-value
t1.5		C	A		C/C	C/A	A/A			C	A		C	A	
t1.6 rs4781678	SZ	923	519	0.56	299	325	97	0.75	0.36	408	226	0.91	515	293	0.54
t1.7	CT	963	517		321	321	98		0.349	420	228		543	289	
t1.8		C	T		C/C	C/T	T/T			C	T		C	T	
t1.9 rs6498567	SZ	814	632	0.5	226	362	135	0.58	0.437	347	289	0.26	467	343	0.96
t1.10	CT	851	627		249	353	137		0.424	372	272		479	355	
t1.11		T	G		T/T	T/G	G/G			T	G		T	G	
t1.12 rs2242549	SZ	762	690	0.61	196	370	160	0.35	0.475	324	316	0.22	438	374	0.69
t1.13	CT	793	691		221	351	170		0.466	352	298		441	393	
t1.14		C	T		C/C	C/T	T/T			C	T		C	T	
t1.15 rs881803	SZ	689	761	0.66	159	371	195	0.47	0.475	320	318	0.13	369	443	0.49
t1.16	CT	694	794		168	358	218		0.466	298	352		396	442	
t1.17		C	T		C/C	C/T	T/T			C	T		C	T	
t1.18 rs2075512	SZ	714	736	0.51	174	366	185	0.51	0.492	316	324	0.87	398	412	0.49
t1.19	CT	751	737		197	357	190		0.505	324	326		427	411	
t1.20		C	T		C/C	C/T	T/T			C	T		C	T	
t1.21 rs2384933	SZ	936	516	0.54	298	340	88	0.71	0.355	414	226	0.68	522	290	0.64
t1.22	CT	976	512		321	334	89		0.344	428	222		548	290	
t1.23		G	A		G/G	G/A	A/A			G	A		G	A	
t1.24 rs11130	SZ	699	741	0.55	162	375	183	0.07	0.485	313	323	1	386	418	0.43
t1.25	CT	738	748		197	344	202		0.497	320	330		418	418	

spectrum disorders in female was not associated with SZ either in male and female (permutation $p=0.90$, 0.054, respectively) of the Japanese population.

Although an association between specific haplotypes of NDE1 and a broad spectrum of SZ specific females was reported (Hennah et al., 2007), we could not replicate significant associations between seven NDE1 SNPs and SZ in our Japanese samples. Different results between our study and Hennah's study may be that (a) different end-state diagnosis subjects used; Hennah et al used a broad spectrum of SZ including SZ, schizoaffective disorder, schizophrenia spectrum conditions and mood disorder, (b) ethnic difference, different allele frequency and different LD patterns (Supplementary Table), (c) different sample size.

In conclusion, we failed to find the association between the NDE1 gene and SZ in the Japanese population. This gene may not play a major role in the etiology of SZ. However we can not rule out a possibility that DISC1-NDE1 interaction may be involved in the etiology of schizophrenia. Further studies will be needed to conclude whether DISC1-NDE1 interaction is associated with SZ.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.schres.2007.10.032.

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BRIEF REPORT

Abnormal microstructures of the basal ganglia in schizophrenia revealed by diffusion tensor imaging

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Abstract

There has been a hypothesis that deficits in the basal ganglia–thalamic system may play an important role in the dysfunctional goal-directed behaviour in schizophrenia. By using diffusion tensor imaging, we measured fractional anisotropy (FA) values in the basal ganglia–thalamic system in 42 schizophrenics and 42 matched controls to investigate microstructural tissue alterations in the basal ganglia–thalamic system in schizophrenia. Schizophrenics had significantly lower FA values in the bilateral globus pallidus and left thalamus compared to controls, suggesting that schizophrenics might have microstructural abnormalities in globus pallidus and thalamus. These data support the notion that myelination abnormalities in basal ganglia–thalamic system are related to the pathophysiology of schizophrenia.

Key words: *Schizophrenia, diffusion tensor imaging, basal ganglia, globus pallidus, MRI*

Introduction

Schizophrenia often demonstrated movement abnormalities, such as catatonia, pacing and other stereotyped behaviours considered to be associated with basal ganglia dysfunction. The basal ganglia regulates not only motor behaviours but also aspects of cognitive and limbic behaviours. There has been a hypothesis that deficits in the basal ganglia–thalamic system may play an important role in the dysfunctional goal-directed behaviour in schizophrenia (Andreasen 1999). In fact, several studies demonstrated abnormalities in the basal ganglia in schizophrenic brains, including the volume reductions of the pallidum internum of postmortem brains of patients with schizophrenia (Bogerts et al. 1985), higher volumes in the globus pallidus of previously treated patients with schizophrenia than the healthy comparison subjects and the neuroleptic-naive patients (Gur et al. 1998), fMRI evidence for basal ganglia dysfunction in subjects with schizophrenia (Menon et al. 2001), abnormality of oligodendroglial cells in caudate nucleus in schizophrenia (Uranova et al. 2001), and positive correlation between globus pallidus and the severity of global symptoms in neuroleptic-naive patients (Spinks et al. 2005).

Diffusion tensor imaging (DTI) is a relatively new technique, and it is useful for evaluating white matter abnormalities in schizophrenia. We have reported progressive changes of white matter integrity in schizophrenia using DTI (Mori et al. 2007).

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Recently, this technique was applied to investigate abnormalities of the subcortical regions in neurodegenerative diseases. Patients with Parkinson's disease had significantly decreased fractional anisotropy (FA) in the region of interest along a line between the substantia nigra and the lower part of the putamen/caudate complex, in which the nigrostriatal dopaminergic neurons are lost in Parkinson's disease, demonstrating its possibility to detect microstructural tissue alterations (Yoshikawa et al. 2004). To investigate possible microstructural abnormalities in the basal ganglia–thalamic system in schizophrenia, we measured FA values in the basal ganglia and the thalami in schizophrenics and in normal controls for comparison, as a sub-analysis of our previous study (Mori et al. 2007).

Material and methods

Subjects and clinical assessments

Forty-two patients with DSM-IV schizophrenia (26 male and 16 female, one left hander, mean age: 40.0 ± 9.3 years old, education: 13.0 ± 2.9 years, mean duration of illness; 16.8 ± 9.0 years, mean daily dose of antipsychotics (chlorpromazine equivalent): 1005.1 ± 735.3 mg/day) (Association 1994) and 42 controls (26 male and 16 female, one left hander, mean age: 39.2 ± 9.0 years old, education: 17.1 ± 3.5 years) were participated in our study. Written informed consent was obtained from all the subjects. This study has been approved by the local ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All the normal subjects were screened by a questionnaire on medical history and excluded if they had neurological, psychiatric or medical conditions that could potentially affect the central nervous system. We employed the Japanese version of National Adult Reading Test (JART) as a convenient tool to measure IQ for participants (premorbid IQ for schizophrenics). Patients had fewer years of education (two-sample t-test, $P < 0.0001$), lower scores of JART (controls: 78.8 ± 11.5, schizophrenics: 58.7 ± 25.3, two-sample t-test $P < 0.001$).

Neuroimaging analysis

MR studies were performed on a 1.5-Tesla Siemens Magnetom Vision Plus system. Axial DTI scans aligned to the plane containing anterior and posterior commissures were acquired with a pulsed-gradient, spin-echo, single-shot echo planar imaging (EPI) sequence (TR/TE = 4000/100 ms, 256 × 256 matrix, FOV 240 mm, $b = 1000$ s/mm^2, NEX = 4, 20 slices, 5 mm slice thickness, 1.5 mm gap). Diffusion was measured along six non-collinear directions, because six directions were maximum number of this Vision Plus system. For each of six gradient directions, four acquisitions were averaged. Four acquisitions without diffusion weighting ($b = 0$) were also averaged. Additionally, a three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence with a gapless series of thin sagittal sections using an MPRage sequence (TR/TE = 11.4/4.4 ms; flip angle, 15°; acquisition matrix, 256 × 256; NEX = 1, FOV 315 mm; slice thickness 1.23 mm) was acquired for evaluating the volume of grey matter (GM), WM and cerebrospinal fluid (CSF) space. Seven diffusion images acquired as above by an in-house script described previously (Mori et al. 2007) on Matlab 6.5 software (Mathworks, Inc., MA, USA). Then, the FA images were spatially normalized using high-dimensional-warping algorithm (Ashburner et al. 1999) and were matched to the FA template image (Figure 1, top). To make the FA template image, we warped FA images of four normal subjects (other than 42 control subjects) to the single-subject T1 template (skull stripped image) using spatial normalization function of SPM2 and averaged the four warped FA images. The transformed FA images were smoothed with a Gaussian kernel (the filter size, full-width half-maximum: 6 × 6 × 6 mm).

Since our interest was FA changes in the basal ganglia and thalamus, we excluded other brain areas by using an explicit mask (Figure 1, top). The resultant FA maps were analyzed using Statistical parametric mapping 2 (SPM2), which implements a 'general linear model'. To test hypotheses about regional population effects, data were analyzed by a two-sample t-test without global normalization. JART scores were treated as nuisance variables. Furthermore, we performed correlational analyses between duration of illness, age of onset, total daily dose of antipsychotic drugs (chlorpromazine equivalent) and FA value in the schizophrenics. Our a priori hypothesis is limited to the basal ganglia; however, investigation of the FA changes within this ROI is null hypothesis. Thus, we used $P < 0.05$, corrected for multiple comparisons with Family–Wise Error rate (FWE) within basal ganglia as a statistical threshold.

Results

In comparison with controls, schizophrenics had significantly lower FA values in the bilateral globus pallidus (GP) (Figure 1, bottom). Increased FA values in schizophrenics were not found in any regions (data not shown).

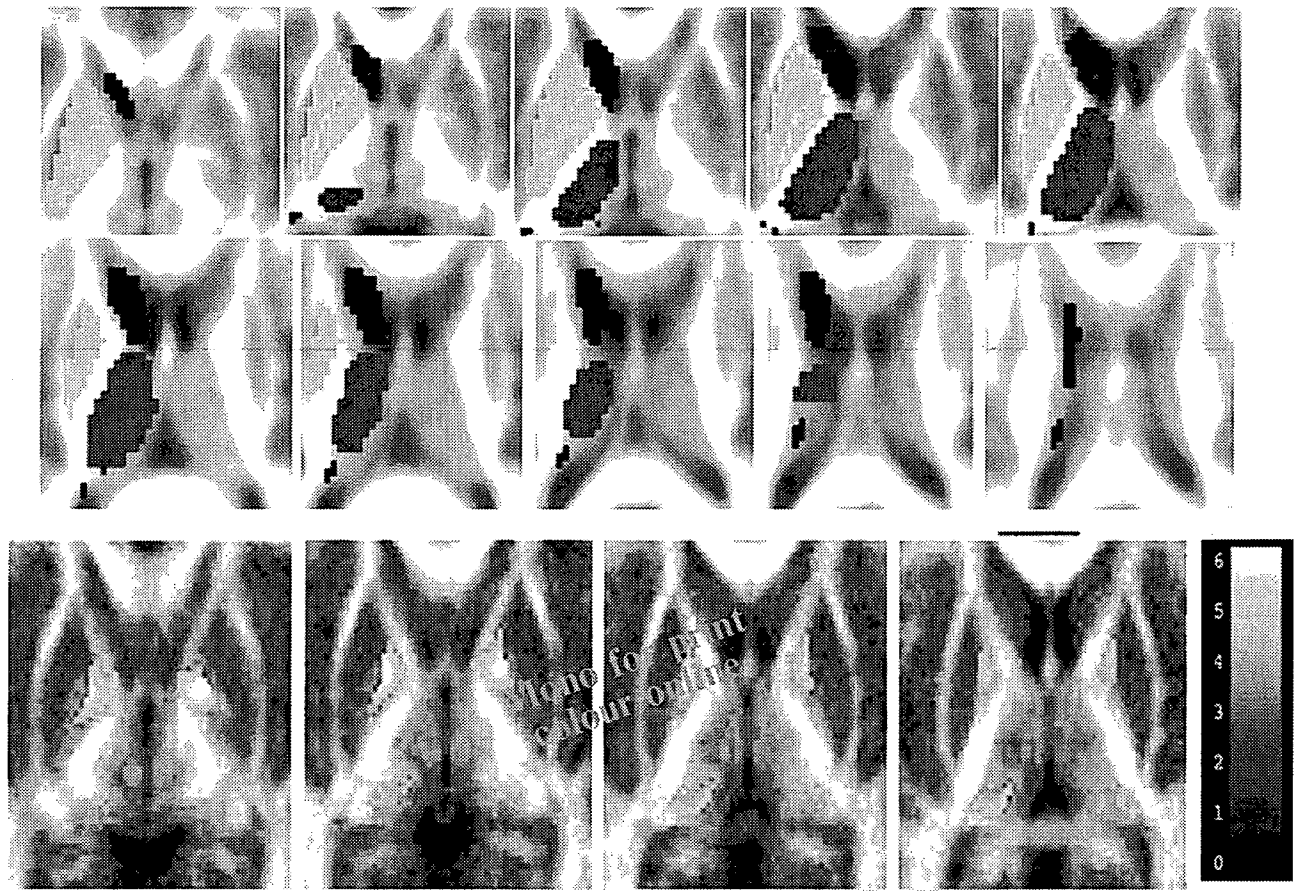

Figure 1. Top: A half of the explicit mask is displayed onto mean FA images of warped FA images obtained from 42 controls (dark blue: caudate nucleus; yellow: putamen; light blue: globus pallidus; red: thalamus). Even after averaging, the mean images are not blurred. Since globus pallidus is traversed by numerous myelinated nerve fibres, it shows higher FA value than other parts of basal ganglia. Bottom: The SPM {t} is displayed onto mean axial FA images of 42 schizophrenics. A significant reduction of FA value in schizophrenia was noted in the bilateral globus pallidus (right GP: t value = 6.52, Talairach coordinate x, y, z: 18, −2, −2, left GP: t value = 6.37, Talairach coordinate x, y, z: −18, −3, −2) and left thalamus (t value = 4.96, Talairach coordinate x, y, z: −18, −33, 10).

A correlational analysis in the schizophrenics demonstrated a significantly negative correlation between duration of illness and FA in the left head of the caudate nucleus (t value = 4.77, Talairach coordinate x, y, z: −11, −17, −6). However, there is no significant correlation between duration of illness and FA values in the GP and the thalamus. There was no significant correlation between FA values in the basal ganglia–thalamic system with age of onset or total daily dose of antipsychotic drugs.

Discussion

In this study, we found a significantly reduced FA value in the bilateral GP and left thalamus in schizophrenics compared to controls. We consider that reduced FA may reflect microstructural abnormalities in the basal ganglia–thalamic system in schizophrenia. A previous fMRI study suggested that GP itself may be the primary locus of the functional deficits in the basal ganglia and may be dysfunctional in schizophrenia (Menon et al. 2001). A postmortem study of basal ganglia morphology reported that only the GP were smaller in schizophrenics than in controls (Bogerts et al. 1985). These studies indicated functional and structural abnormalities in GP in schizophrenia. Our data, reduced FA in GP in schizophrenia, were obtained using a size-adjusted high-dimensional warping method (Ohnishi et al. 2006). Our results, microstructural abnormalities in the GP in schizophrenia, are consistent with previous reports.

Although the underlying mechanisms remain to be clarified, previous DTI studies in parkinsonism have well demonstrated ongoing pathological changes in neurodegenerative diseases, suggesting that this technique has the potential to detect microstructural alterations in the basal ganglia (Yoshikawa et al. 2004). Since pathological findings of schizophrenia are still ambiguous, the underlying pathological changes of reduced FA values in schizophrenia are unclear. However, multiple lines

of evidence now converge to implicate oligodendroglia and myelin in schizophrenia (Davis et al. 2003). We assume that damage of myelinated nerve fibres may contribute to FA reduction in the basal ganglia–thalamic system. The GP is traversed by numerous myelinated nerve fibres that give it the pale appearance for which it is named, and has rich connections to the putamen and the thalamus. These histological characteristics of the GP may contribute to its higher FA values. A qualitative electron microscopic study reported the density of concentric lamellar bodies (an indicator of damage of myelinated fibres) was dramatically increased in the caudate nucleus in schizophrenia, as compared to controls (Uranova et al. 2001). Such pathological changes seem to explain decreased FA values in the schizophrenic brain. However, there have been no data on whether GP also have alterations of myelinated fibres. Further pathological studies need to be conducted to draw a firm conclusion on this matter.

Although some studies demonstrated abnormalities of GP in neuroleptic-naïve schizophrenics (Spinks et al. 2005), abnormalities in the basal ganglia have been considered to relate to antipsychotic medication (Gur et al. 1998). In this study, FA changes in the GP and thalamus were not associated with the duration of illness or the daily dose of antipsychotic drugs, suggesting that FA changes in these regions might be independent of medication with neuroleptics. Guidelines for the biological treatment of schizophrenia developed by an international Task Force of the World Federation of Societies of Biological Psychiatry recommended atypical antipsychotics as first line drugs (Falkai et al. 2005, 2006). The differential treatment effects on brain morphology could be due to typical antipsychotics-associated toxicity or greater therapeutic effects of atypical antipsychotics (Lieberman et al. 2005). It would be interesting to compare patients treated with atypical antipsychotics to those with a history of typical antipsychotics treatment; however; the subgroup of patients that were only treated with atypical antipsychotics or the subgroup of patients that were only treated with typical antipsychotics were too small to investigate a possible difference between two groups in FA in our sample. To conclude whether observed change of FA value is a result of medication or relates to the pathophysiology of schizophrenia itself, longitudinal studies on treated schizophrenics, and studies on neuroleptic-naive schizophrenics should be conducted.

There is a limitation to our study: we used a 1.5-Tesla Siemens Magnetom Vision Plus system, which is a relatively old system. We chose six gradient directions, which is quite low, as this number is the maximum number of directions in this system. Slice thickness of 5 mm and 1.5-mm slice gaps are methodological drawbacks to this study. The reason why we used a slice thickness of 5 mm and 1.5-mm slice gaps is to cover the whole brain as in our previous study (Mori et al. 2007). There may be a partial volume effect in our mapping parameters, although we minimized the problem by using the high-dimensional warping algorithm.

Our data suggest that patients with schizophrenia might have microstructural abnormalities in globus pallidus and thalamus. The DTI study may be a promising method to investigate microstructural abnormalities in schizophrenia.

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Title: Personality in schizophrenia assessed with the Temperament and Character Inventory (TCI)

Article Type: Research Article

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Keywords: schizophrenia; personality; temperament; character; gender difference

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Abstract: The Temperament and Character Inventory (TCI) is a well-established self-report questionnaire measuring 4 temperament and 3 character dimensions. However, surprisingly few studies have used it to examine the personality of patients with schizophrenia, and none in Japan. Moreover, possible gender differences in personality among patients with schizophrenia have not been well documented. We administered the TCI to 86 Japanese patients with schizophrenia and age- and gender-matched 115 healthy controls to characterize personality traits in patients with schizophrenia and to examine their relationships with clinical variables, particularly gender and symptoms. Compared to controls, patients demonstrated significantly lower novelty seeking, reward dependence, self-directedness and cooperativeness, and higher harm avoidance and self-transcendence. Male patients showed even more pronounced personality alteration than female patients when both of them were compared to healthy people. Personality dimensions were moderately correlated with symptom dimensions assessed by the Positive and Negative Syndrome Scale (PANSS). These results, together with prior findings in several other countries, suggest that

schizophrenia patients have a unique personality profile which appears to be present across cultures and that the greater alteration of personality in schizophrenia males might be related to their poorer social and community functioning.

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May 11, 2007

Re: Personality in schizophrenia assessed with the Temperament and Character Inventory (TCI) (PSY-D-07-00096)

Dear Prof. Buchsbaum:

Thank you for providing us with an opportunity to resubmit our manuscript. We are also very grateful to the anonymous referee for valuable comments. According to the comments, we have revised our manuscript. Please refer to the answers to the referees on separate sheets. I hope that the revised version will be suitable for publication in *Psychiatry Research*.

We are looking forward to hearing from you in due course.

Sincerely,

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Answers to the editors' requirements:

Comment 1 In addition to the points raised by the reviewers, please carefully review the Guide to Authors on our website. It would be also be useful for you to review the articles contained in the sample issue on our website for examples of title page format, heading typography, and other style features.

Answer: According to the editors' comments, we have revised the manuscript as carefully as we can, based on the stylistic requirements of the *Journal*.

Comment 2 We also thought the ms needs to be shortened. You can easily combine Tables 1 and 2. It also appears that the figure duplicates the data in Table 3. Please chose one or the other.

Answer: According to the comment, we have combined the previous Tables 1 and 2 into a new table, Table 1, and removed the data on male vs. female comparisons from Table 3 since the similar data are, as pointed out by the editors, also presented in Fig. 1. Descriptions on the gender difference in the Results section have been modified accordingly (L4-19, P11).

Answers to the reviewer #1:

Comment 1 The introduction might say more about what exactly studies have previously found. What symptoms have been linked with what personality dimensions and what was made of that by previous authors? This should be spelled out as it is the context in which the authors should later interpret the results. The literature on this subject could also be more broadly noted and cited.

Answer: According to the reviewer's comment, we have increased the descriptions on what previous studies have found regarding the following issues: relationships between symptoms and personality dimensions (L14-20, P4), variability of personality as assessed with the TCI across cultures (L18-21, P3), and various aspects of gender difference unfavorable to male patients (L3-6, P5). Furthermore, several relevant references have been added to the Introduction section.

Comment 2 The introduction might say more about what specific previously unaddressed or under studied questions this study seeks to explore. What is the gap these finding intend to fill besides just using another instrument.

Answer: The questions we had considered unaddressed or under studied were gender difference and cross-cultural comparisons of personality in schizophrenia, and comparisons of TCI and NEO-FFI findings in schizophrenia. In addition, we thought that the relationships between symptoms and personality in schizophrenia remain to be further examined. According to the helpful comment, we have clearly stated the gaps this study intended to fill regarding these questions (L21, P3 to L1, P4; L9-13, P4; L20, P4 to L1, P5; L6-8, P5).

Comment 3 The introduction could include they study hypotheses. What was anticipated?

Answer: According to the helpful comments, we have added 3 hypotheses that correspond to the aims of this study (L13-19, P5).

Comment 4 I would not use the word deviant when referring to the personality of the sample. "Deviant" can have a very negative connotation, implying in some senses criminality or antisocial tendencies which certainly is not what the authors intend.

Answer: We have now realized that "deviant" has a very negative connotation which we were at first unaware of. Therefore, we have changed the word "deviant" into "altered" or "unique", and "deviance" into "alteration" throughout the manuscript.

Comment 5 The discussion could be condensed and re-organized around the study hypotheses once laid out in the introduction.

Answer: According to this comment, we have re-organized the discussion section, focusing on the 3 hypotheses laid out earlier. Furthermore, we have explicitly

described whether the hypotheses have been supported (L13, P15; L17-19, P15; L5-7, P17). The speculative discussion on causal relationships between personality and development of schizophrenia has been deleted.

Comment 6 Results could also be linked back more carefully to the results of studies using other methods of personality assessment as noted in the introduction.

Answer: According to the helpful comment, we have added the detailed descriptions on comparisons between the present TCI results and previous findings from NEO studies in the Discussion section (L19, P14 to L13, P15).

Personality in schizophrenia assessed with the Temperament and Character Inventory (TCI)

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Abstract

The Temperament and Character Inventory (TCI) is a well-established self-report questionnaire measuring 4 temperament and 3 character dimensions. However, surprisingly few studies have used it to examine the personality of patients with schizophrenia, and none in Japan. Moreover, possible gender differences in personality among patients with schizophrenia have not been well documented. We administered the TCI to 86 Japanese patients with schizophrenia and age- and gender-matched 115 healthy controls to characterize personality traits in patients with schizophrenia and to examine their relationships with clinical variables, particularly gender and symptoms. Compared to controls, patients demonstrated significantly lower novelty seeking, reward dependence, self-directedness and cooperativeness, and higher harm avoidance and self-transcendence. Male patients showed even more pronounced personality alteration than female patients when both of them were compared to healthy people. Personality dimensions were moderately correlated with symptom dimensions assessed by the Positive and Negative Syndrome Scale (PANSS). These results, together with prior findings in several other countries, suggest that schizophrenia patients have a unique personality profile which appears to be present across cultures and that the greater alteration of personality in schizophrenia males might be related to their poorer social and community functioning.

Keywords: Schizophrenia; Personality; Temperament; Character; Gender difference

1. Introduction

Personality in schizophrenia has been of interest ever since the pioneering intuition of Bleuler (1950) and Kraepelin (1919). Personality is considered to be an important aspect of schizophrenia primarily because it may influence symptom expression (Lysaker et al., 1999; Guillem et al., 2002) and social functioning (Lysaker et al., 1998; Eklund et al., 2004).

The Temperament and Character Inventory (TCI, Cloninger et al., 1993) is a well-established self-report questionnaire measuring 4 temperament and 3 character dimensions, developed on the basis of a psychobiological model of personality. The TCI has recently been widely used in personality studies in various psychiatric disorders including mood disorders (Hansenne et al., 1999; Cloninger et al., 2006) and personality disorders (Svrakic et al., 1993; Svrakic et al., 2002). However, to our knowledge, only three studies (Guillem et al., 2002; Boeker et al., 2006; Calvo de Padilla et al., 2006) have examined the personality of schizophrenia patients in comparison with healthy controls, using the TCI. The findings from these studies on unique personality profiles of schizophrenia are, to some extent, consistent with each other; but the limited sample sizes of the studies have made it difficult to draw definitive conclusions. It is also possible that cultural differences of personality between these studies exist, taking into account that personality traits among general population as measured by the TCI vary across cultures (Pélissolo and Lépine, 2000; Brändström et al., 2001). Such

cross-cultural comparison of personality in schizophrenia is an under-studied topic.

The knowledge to date on personality of schizophrenia patients has been based mostly on instruments other than the TCI (Malmberg et al., 1998; Lysaker et al., 1999; Gurrera et al., 2000; Van Os and Jones, 2001; Pillmann et al., 2003). A number of studies have been done to investigate personality in patients with schizophrenia by using the well-known NEO Five-Factor Inventory (NEO-FFI, Costa and McCrae, 1992), the results from which are fairly consistent; higher neuroticism and lower extraversion and conscientiousness in schizophrenia patients than in healthy controls (Gurrera et al., 2000; Pillmann et al., 2003; Camisa et al., 2005). Given the close relationship of the TCI dimensions to the "Big Five" personality dimensions of the NEO-FFI (De Fruyt et al., 2000; MacDonald and Holland, 2002; Ramanaiah et al., 2002), it would be intriguing to examine whether the personality of schizophrenia patients as assessed by the TCI shows a compatible pattern with that assessed by NEO-FFI.

Concerning the association between personality and symptom dimensions in schizophrenia, previous studies that employed the TCI (Guillem et al., 2002) as well as NEO-FFI (Lysaker et al., 1999) found certain relationships between these two dimensions; for example, Guillem et al. (2002) reported that psychotic symptoms in schizophrenia patients were associated with specific personality dimensions of the TCI. Boeker et al. (2006), by contrast, did not find any relationships between personality and symptoms although the sample size of this study was relatively small. Due to the paucity of material, the association between personality and symptoms in schizophrenia

remains to be further clarified.

Gender difference in essential facets of a particular disorder can yield important clues to its pathogenesis. In schizophrenia, gender differences have been shown in premorbid functioning, age at onset, symptomatology, and neuropsychological functioning. In general, male patients are reported to show indications of severer illness than female counterparts (Castle et al., 1993; Leung and Chue, 2000). However, possible gender differences in personality among patients with schizophrenia have not been well documented.

In this context, the present study aimed (1) to characterize personality traits in Japanese patients with schizophrenia using the TCI and compare the results with findings from the prior TCI as well as the NEO-FFI studies, and (2) to examine whether personality is related to clinical variables, particularly gender and symptoms, in schizophrenia. The study hypotheses were as follows; (i) Japanese patients with schizophrenia would show a unique personality profile, which is similar to that found in previous TCI studies of other countries as well as NEO studies, (ii) when compared to personality of healthy people, the alteration of personality in male patients would be even greater than that in female patients, as is usually the case with gender differences in schizophrenia, and (iii) the more severe the symptoms are, the more prominent the personality alteration would be.